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Synthesis of Naphthalenes through Three-Component Coupling of Alkynes, Fischer Carbene Complexes, and Benzaldehyde Hydrazones via Isoindole Intermediates

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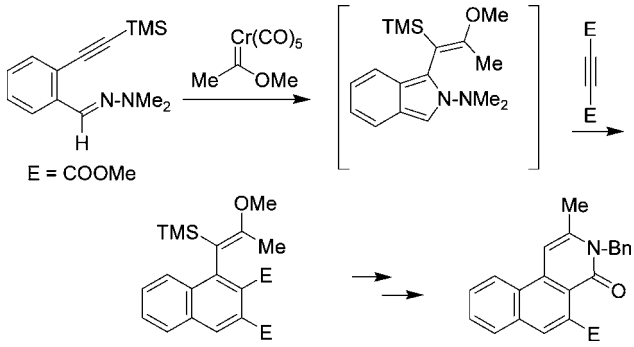
ABSTRACT



The synthesis of naphthalene derivatives through three-component coupling of 2-alkynylbenzaldehyde hydrazones with carbene complexes and electron-deficient alkynes has been examined. The reaction involves formation of an isoindole derivative, followed by intramolecular Diels–Alder reaction, followed by nitrene extrusion. The reaction was highly regioselective using unsymmetrical alkynes.

Substituted naphthalene derivatives have emerged as very important biological entities[1] and frequently are employed as starting materials for the preparation of more complex polynuclear aromatic ring systems.[2] A variety of methods have been reported for their formation;[2] however, the most common strategy is to annulate a second aromatic ring onto a preexisting benzene ring system. Multicomponent coupling reactions offer an incredible level of diversity for the production of diverse structural entities from a few simple components.[3] In this paper, a method that directly produces substituted naphthalenes in a one-pot, three-component coupling process will be presented.

Synthesis of substituted naphthalene derivatives (**E**, Scheme 1) using alkynylbenzaldehydes (**A**, Y = O), Fischer carbene complexes (**B**), and electron-deficient alkenes was recently presented.[4] This process involves generation of an isoben-

(1) Some representative examples from this century include: (a) Dalton King, H.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Epperson, J. R.; Higgins, M. A.; Kung, J. E.; Marcin, L. R.; Sloan, C. P.; Mattson, G. K.; Molski, T. F.; Krause, R. G.; Bertekap, R. L.; Lodge, N. J.; Mattson, R. J.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5647−5651. (b) Wang, Z.; Elokdah, H.; McFarlane, G.; Pan, S.; Antane, M. *Tetrahedron Lett.* **2006**, *47*, 3365−3369. (c) Saeki, K.; Matsuda, T.; Kato, T.; Yamada, K.; Mizutani, T.; Matsui, S.; Fukuhara, K.; Miyata, N. *Biol. Pharm. Bull.* **2003**, *26*, 448−452. (d) Hartmann, R. W.; Palusczak, A.; Lacan, F.; Ricci, G.; Ruzziconi, R. *J. Enz. Inhib. Med. Chem.* **2004**, *19*, 145−155.

(2) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2002**, *59*, 7−36.

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(4) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267−1269.

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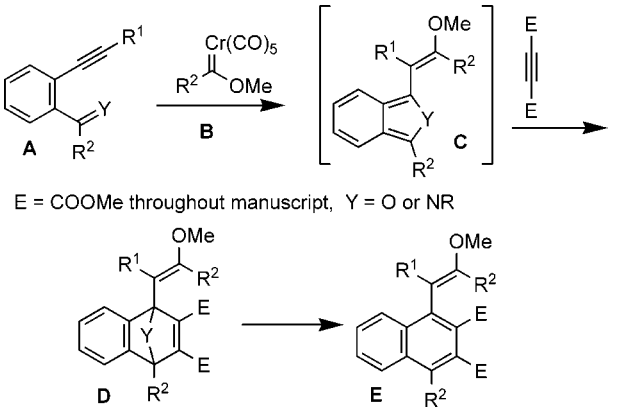
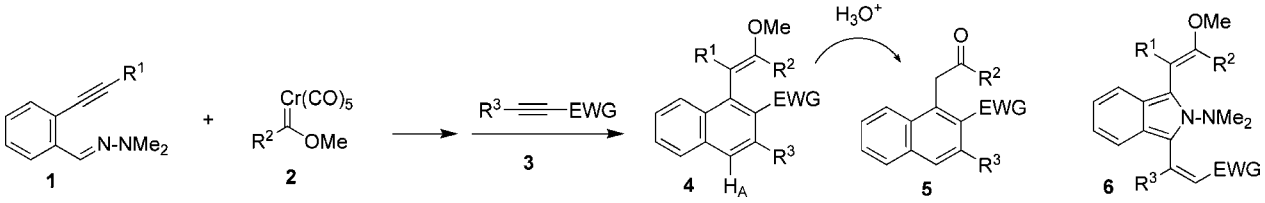
Scheme 1



zofuran (**C**) and Diels−Alder reaction to afford oxanobornene derivatives (**D**), which can subsequently transform to naphthalenes through either dehydration (using alkene dienophiles) or reduction (using alkyne dienophiles). High product yields were limited to systems involving comparatively stable arylisobenzofuran intermediates (R^2 = Ph), which offer sufficient lifetimes such that the carbene−alkyne coupling and Diels−Alder reactions can be conducted in separate events. In theory, if the isobenzofuran intermediate could be stabilized, the versatility of a carbene complex-based naphthalene synthesis could be improved substantially. One potential solution is to employ isoindoles (**C**, Y = NR) in place of isobenzofurans. Isoindoles offer increased stability relative to isobenzofurans yet still offer a high level of reactivity in cycloaddition processes.[5] In cases where the nitrogen of a pyrrole or isoindole ring contains an amino group, then azanorbornenes produced in the Diels−Alder reactions can undergo nitrene extrusion reactions to directly afford aromatic systems.[6] Aminoisoindoles have limited precedent in cycloaromatization reactions.[7]

The three-component coupling of hydrazone **1a**, methylcarbene complex **2a**, and DMAD (**3a**) was tested initially (Table 1, entry A-1). This reaction led to the naphthalene derivative **4a** in high yield as the exclusive product of the reaction. The reaction was next attempted with the less activated alkyne ethyl propiolate (entries B-1, 2). This cycloaddition reaction was considerably lower yielding but was completely regioselective for the depicted isomer, **4b**. The yield was not improved by the addition of a larger excess of ethyl propiolate (**3b**). The regiochemistry was easily assigned based on the appearance of isolated doublets (J = 8.3 Hz) at δ 7.77 and δ 7.68. Use of ethanol as the solvent led to the deep red Michael addition product **6b** and not the cycloaddition/nitrene extrusion product **4b** (entry B-3). This reaction pathway has been observed primarily for pyrrole derivatives and in a few cases for isoindoles.[8] Both *N*-aminopyrroles and *N*-aminoisoindoles however engage primarily in cycloaddition reactions with acetylenic esters.[9] A similar reaction using DMAD in ethanol also led to the Michael addition product **6a** as a mixture of stereoisomers (entry A-2). Formation of **4** and **6** in the different solvents likely reflects solvent polarity. The nonpolar Diels−Alder reaction occurs in dioxane and the polar Michael addition pathway in ethanol. The alkynyl ketone derivative **3c** underwent a similar cycloaddition reaction in higher yield than the corresponding ester (see entry C). The silylated alkyne analogue **3d**, however, was not a suitable dienophile

Table 1. Three-Component Coupling of Benzaldehyde Hydrazones, Carbene Complexes, and Alkynes



entry[a,b]	reactants	R^1	R^2	EWG	R^3	solvent[c]	yield of **4**[d] (%)	yield of **6** (%)
A-1	**1a** + **2a** + **3a**	TMS	Me	E	E	dioxane	90 (98)	
A-2	**1a** + **2a** + **3a**	TMS	Me	E	E	ethanol	0	79
B-1	**1a** + **2a** + **3b**	TMS	Me	COOEt	H	dioxane	30	
B-2[e]	**1a** + **2a** + **3b**	TMS	Me	COOEt	H	dioxane	10	
B-3	**1a** + **2a** + **3b**	TMS	Me	COOEt	H	ethanol	0	65
C	**1a** + **2a** + **3c**	TMS	Me	COPh	H	dioxane	72	
D	**1a** + **2a** + **3d**	TMS	Me	COPh	TMS	dioxane	0	
E	**1a** + **2b** + **3a**	TMS	1-cyclohexenyl	E	E	dioxane	72	
F	**1b** + **2b** + **3a**	H	1-cyclohexenyl	E	E	dioxane	75	
G	**1a** + **2c** + **3a**	TMS	Ph	E	E	dioxane	95 (46)	
H	**1a** + **2d** + **3a**	TMS	-$(CH_2)_2CH{=}CH_2$	E	E	dioxane	86	
I	**1a** + **2a** + **3e**	TMS	Me	CH=CHCOOEt	COOEt	dioxane	85	

[a] Table entry letters correlate with substituent identifiers for compounds **4**−**6**. [b] Unless otherwise stated, the hydrazone, carbene complex, and dienophile were used in a 1.0:1.3:5.0 ratio. [c] Reactions in dioxane were conducted at 80 °C; reactions in ethanol at reflux. [d] The yield in parentheses is the yield for hydrolysis to form ketone **5**. [e] In this experiment, 20 equiv of ethyl propiolate was employed.

(entry D). The Dötz benzannulation reaction[10] does not compete as noted by the successful three-component couplings using α,β-unsaturated carbene complexes **2b**,**c** (entries E−G) and no formation of naphthalenes **8** or **9** (Figure 1).

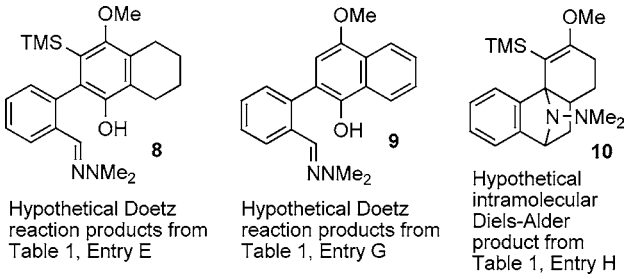
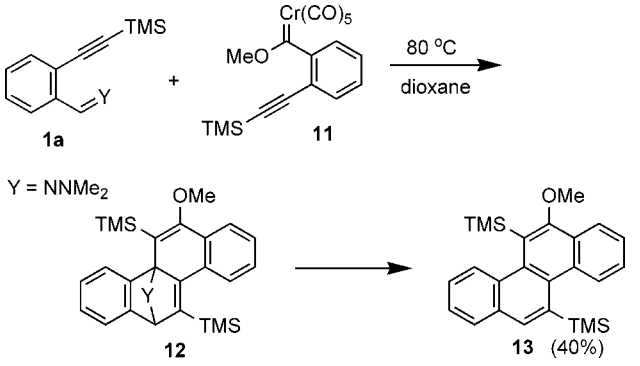


Figure 1. Hypothetical side products from the reactions in Table 1.

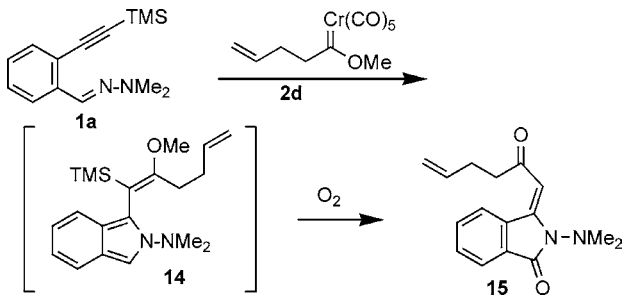
Use of the γ,δ-unsaturated carbene complex **2d** led to none of the intramolecular Diels−Alder adduct **10**; however, the isoindole could be efficiently trapped using DMAD (entry H). Use of the enyne diester dienophile **3e** led to the naphthalene derivative **4i** in high yield as a single regioisomer (entry I). Although the directly attached ester is intuitively the stronger electron-withdrawing group, in related Diels−Alder processes using enyne **3e** the alkene acts as the stronger electron-withdrawing group.[11] This regiochemical assignment was based on the appearance of a cross-correlation for the naphthalene singlet (H_A) and a carbonyl group in the HMBC spectrum. Although unactivated alkynes were not suitable dienophiles for the three-component naphthalene synthesis, their use in intramolecular couplings was successful (Scheme 2). Coupling of alkynylphenylcarbene complex **11** with alkyne hydrazone **1a** led to the chrysene derivative **13**.

Scheme 2



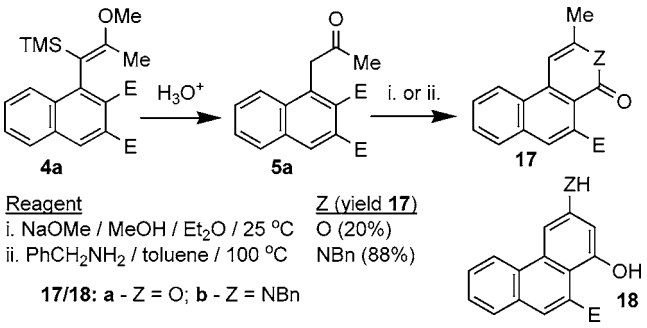
Simple isoindoles are typically unstable and difficult to isolate. An attempt to isolate the isoindole intermediate was conducted (Scheme 3). If the reaction was performed without a dienophile additive, several products were obtained after an attempted chromatographic purification. The major and only identifiable product was the *N*-aminolactam derivative **15** (35% yield), obtained through auto-oxidation of the isoindole intermediate **14**.[12]

Scheme 3



Acid-catalyzed hydrolysis of the DMAD adducts in Table 1 leads to compounds containing multiple carbonyl groups (**5**). The DMAD-adduct **5a** was examined in condensation reactions to test for the possible formation of additional ring system (Scheme 4). Reaction of **5a** with sodium methoxide led only to the lactonization product **17a** and none of the Claisen condensation product, phenanthrenediol derivative **18**. Apparently enolate generation occurs exclusively at the more acidic[13] benzylic position and thus none of the anticipated thermodynamic product **18** arising from deprotonation of the methyl ketone group of **5a** was ever observed.

Scheme 4



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Similarly, treatment of **5a** with benzylamine led only to the pyridone derivative **17b**. The 2-azapyridine ring system has been evaluated for cytotoxic and antiinflammatory properties.[14] This represents a potentially diverse route to this ring system.[15]

In summary, a new three-component coupling reaction for the synthesis of naphthalene derivatives has been presented. The reaction provides richly functionalized naphthalenes that can undergo further annulation reactions to afford 2-azaphenanthrene ring system. The reaction can be diverted toward the production of stable isoindole derivatives through a change of the solvent from dioxane to ethanol. Reactions employing alkynylated carbene complexes afford chrysene rings in a single step in a net [5 + 5]-cycloaddition−nitrene extrusion process.

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Supporting Information Available: Complete experimental procedures and compound characterization data for compounds **4a**−**c**,**d**−**i**, **5a**,**g**, **13**, **15**, and **17a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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